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Role of Crystallization in Genesis of Diverse Crystal Forms of Antidiabetic Agents

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Additional information is available at the end of the chapter

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1. Introduction

Crystallization is a crucial step in the manufacturing and processing of active pharmaceutical ingredients (API's) in pharmaceutical industry [1]. As crystallization is coupled with molecular recognition, a slight alteration in crystallization conditions can affect crystal and powder properties accompanied with thermodynamic and mechanical properties [2]. So, the selection of an appropriate solid form of an active pharmaceutical ingredient (API) in the early stages of drug development is very important as it can be pure crystalline form or its non covalent modification such as polymorph, amorphate, hydrate, solvate, salt or co-crystals exhibiting unique physicochemical properties (solubility, dissolution rates, stability and bioavailability) and other performances characteristics of drug [3].

Existence of a crystalline solid into many crystalline forms leads to polymorphism which is a phenomenon, hard to predict. It may be of two types either conformational (due to existence of various conformers of molecule) or packing polymorphism (due to difference in crystal packing). On thermodynamic consideration, there are also two types of polymorphism i.e., monotropic system (when the transition of one form to another is irreversible) and enantiotropic system (reversible forms) [4]. In general, least stable crystal form crystallizes out first, not the most stable form. Metastable crystal form (unstable) tend to change to more stable form under particular conditions [5]. Crystal forms are the entities which are similar at molecular level but dissimilar in supramolecular aspect [6].

The various conditions used in the process of crystallization is the chief cause of generation of different crystal forms of a molecule and the difference in the properties of various crystal forms is due to different crystal packing and lattice energy [4]. Advancement in synthesis has gained control on the synthesis and purity of drugs but still lag behind in controlling the

crystallinity and physical crystal forms. Different forms of a crystalline solid can be controlled by controlling the crystallization process.

The best method used for obtaining the variety of crystal forms is crystallization as it is traditional, easy and unbeatable process. Crystallization techniques may be solvent or non-solvent based and varied methods give rise to different forms. Solvent crystallization techniques include solvent evaporation, slow cooling of the solution, diffusion, vapour diffusion while non solvent techniques include sublimation, thermal treatment, desolvation of solvates, grinding and crystallization from melt etc. The choice of appropriate technique may be decided depending on the amount of sample and physical stability or solubility of drug [7-8].

Different crystal forms due to different crystal lattice have different physicochemical properties and thus therapeutic effects. Thus, Pharmaceutical companies usually search for a crystal form or polymorph with the best properties for therapeutic use and manufacturability. Selection of an optimized crystal form is of more relevance as regulatory bodies are showing their interest in physico-chemical characterization of APIs. Polymorphism is also important to be considered because this phenomenon is not exhibited by only drug molecule but also by other solid forms prepared by drug using crystal engineering approaches like salts, solvates, co-crystals etc. However, the discovery and genesis of various crystal forms is quite tiresome and expensive [9-12].

This chapter has focused on the various crystal forms of anti-diabetic agents and techniques employed in their preparation.

Diabetes mellitus is an unceasing disease in the society that requires life-long pharmacological and non-pharmacological management. Among this, type 2 diabetes mellitus is more prevalent. For the management of type 2 diabetes mellitus, various oral agents have been approved. The main problem of these agents is their dissolution limited bioavailability. To overcome this issue various attempts like CD complexes, solid dispersion, crystal engineering approaches and exploring the more soluble polymorphic form have been made.

2. Case studies of crystal forms of antidiabetics

Several crystalline forms of anti-diabetics have been described in the past. A general account of different crystal forms, their method of preparation along with transition / melting temperature are detailed in table 1.

3. Sulfonylureas

3.1. Acetohexamide

Potentiality of polymorphism in acetohexamide was first observed by Girgis-Takla and Chronos in 1977. They reported two polymorphic forms (polymorphs A and B), distinguished

by IR spectra and further characterized by Mueller and Lagas. However, forms showed no notable difference on drying at 60°C in vacuum [13-14]. Graf *et al.* proposed keto-enol tautomerism for their stability, confirmed by IR spectra. Polymorph A (enol form) forms six membered ring via bonding of an O—H and S=O group intramolecularly while polymorph B (keto form) shows intermolecular bonding of C=O of urea to a sulphonamide N—H [15-16].

Kuroda *et al.* collected three crystal forms (Form I, Form II and CHCl₃ – II) out of which one was found to be chloroform solvate. Form II was found to be 1.2 times more soluble than Form I [17]. Yokoyama *et al.* estimated the thermodynamic values (transition temperature - 154°C & heat of transition - 230°C) of crystal forms (Form I and Form II) from solubility studies. Both forms were found equally bioavailable in beagle dogs [18]. Another forms Form IV by Graf *et al.* and Form II and III by Al-Saieq and Riley were investigated [19-20]. Later Graf *et al.* found that Form II was mixture of I and IV, while Form III (by Al-Saieq and Riley) on heating, converted to a new polymorph V [15].

Another crystal form of acetohexamide (Form VI) by Aldawsari *et al.* was reported and was more soluble in water, and more bio-available in rats as compared to other already reported crystal forms [21].

3.2. Chlorpropamide

Various publications on the crystal forms (about 16) of chlorpropamide were reported (by Simmons *et al.*, Burger *et al.*, and Saieq *et al.*) [22-24], but the provided data could not distinguish existing crystal forms in actual [1-3]. Ueda *et al.* depicted convex shaped dissolution curve for Form C (by Simmons *et al.*) and Form II (by Saieq *et al.*) that indicates crystallization along with anhydrate to hydrate phase transformation [25].

After that, Debrushchaket *et al.* adopted a new methodology for nomenclature (α , β , γ , δ , ϵ) on the basis of the order of their crystal structure established. Form α , β , γ and δ correspond to previously reported Form III, II, IV and VI respectively and was found that all forms transformed to ϵ (Form I) crystal form. On cooling up to 200 K, crystal form ϵ , converted to another new form (ϵ'). This new form resembled to α form in aspect of cell parameters and molecular conformation while to ϵ form in case of packing (Z shaped ribbons). Form α , β , γ has same intermolecular hydrogen bonding but differ in packing and number of molecules in unit cell [26-30].

Bifurcated intermolecular hydrogen bonding pattern of carbonyl group has been seen with the two amine hydrogen atoms, and SO₂ oxygen atom acquires hydrogen from the nitrogen attached to alkyl tail. With regard to enthalpy of transition, conversion of α , β , γ and δ to ϵ should be in order of $\beta > \gamma > \delta > \alpha$ but β polymorph infracts it because of structural difference [31].

All these polymorphs are conformational polymorphs as they showed difference in torsion angles. (as shown in figure 1) [32]

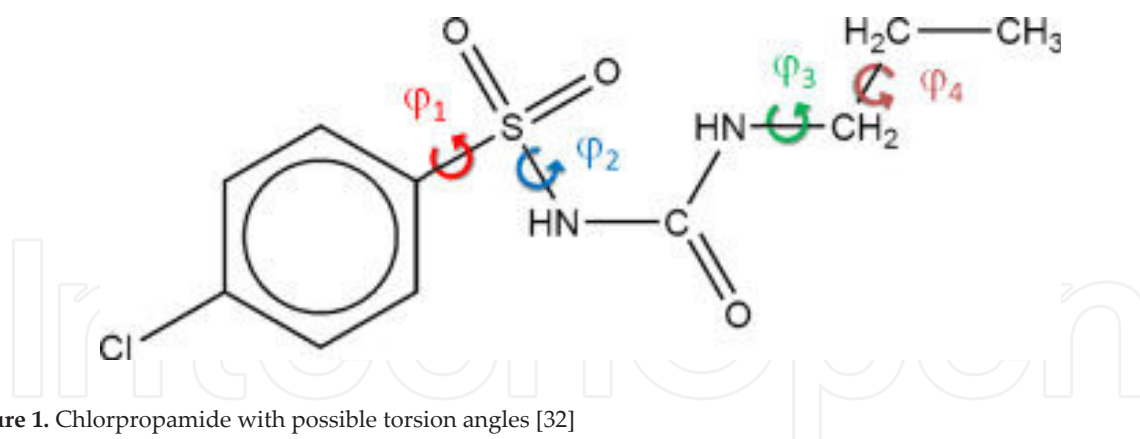


Figure 1. Chlorpropamide with possible torsion angles [32]

Process of crystallization was also found to be affected by the presence or absence of 2-hydroxybutyl- β -cyclodextrin as chlorpropamide crystallized to metastable Form II and III in presence, whereasto Form A in the absence at 4°C. Even the appearance of crystal form was dependent on the concentration and temperature [33].

3.3. Tolbutamide

Several Tolbutamide polymorphs are reported by several groups of workers. [34-42]. Two forms reported by Simmons *et al*[34] (Forms A and B) are identical with the Burger's Form I and III [35], respectively, and have been well characterized. However, Burger's Forms II and IV have been not fully characterized.

3.4. Glimepiride

Two polymorphs (Form I and II) are reported in literature. New crystalline form (Form II) was prepared by recrystallization from an ethanol/water system was found to have different dissolution profile and solubility [43] and it transformed to Form I over 140°C.

3.5. Glibenclamide

Crystallisation of glibenclamide from different solvents and quick cooling of melt gave three polymorphic forms and pseudopolymorphs (solvates), which were significantly different with regard to solubility and melting properties. [44-45] A new crystalline form of glibenclamide, with higher melting point (218°C) and lower solubility, was formed during an attempt to elucidate transitional phases by melting, cooling and reheating by A. Panagopoulou-Kaplani, *et al*[46].

4. Meglitinides

4.1. Nateglinide

Various solvates/ hydrates (about 26) of nateglinide have been patented which eventually converts to either Form B or Form H. [47] The S polymorph was crystallized from the melt or

by isothermal treatment of B or H forms at temperatures higher than their melting points which is the only stable form, while the polymorphs B and H are metastable forms. The anhydrous polymorph, if stored at room temperature and humidity, gradually changes to H polymorph while, if stored in water vapour saturated atmosphere, it gets back water and reverts to the hemihydrate form. On the contrary, both an isothermal treatment at 80 °C and melt cooling bring to the B polymorph [48].

4.2. Repaglinide

S enantiomer of repaglinide was found active hypoglycemic agent and three crystalline forms (Form I, II and III) were crystallized from various solvents by solvent/antisolvent and slow evaporation method. Form II (low melting crystal form) on further heating showed second melting endotherm at 127-130°C and converted to Form I if crystallized in ethanol/water mixture [49].

5. Biguanides

5.1. Metformin hydrochloride

Two polymorphs (form A and B) has been identified out of which form A is more thermodynamically more stable while highly metastable structure, which correlates with the difficulty in handling this polymorph [50]. These two polymorphs and their mixture has been evaluated by Scott L. Childs, *et al* using capillary crystallization and thermal microscopy techniques. Crystal structure of these forms are reported [51]. Both structures are monoclinic (P21/c) with one complete metformin cation and one chloride anion in the asymmetric unit as shown in figure 2.

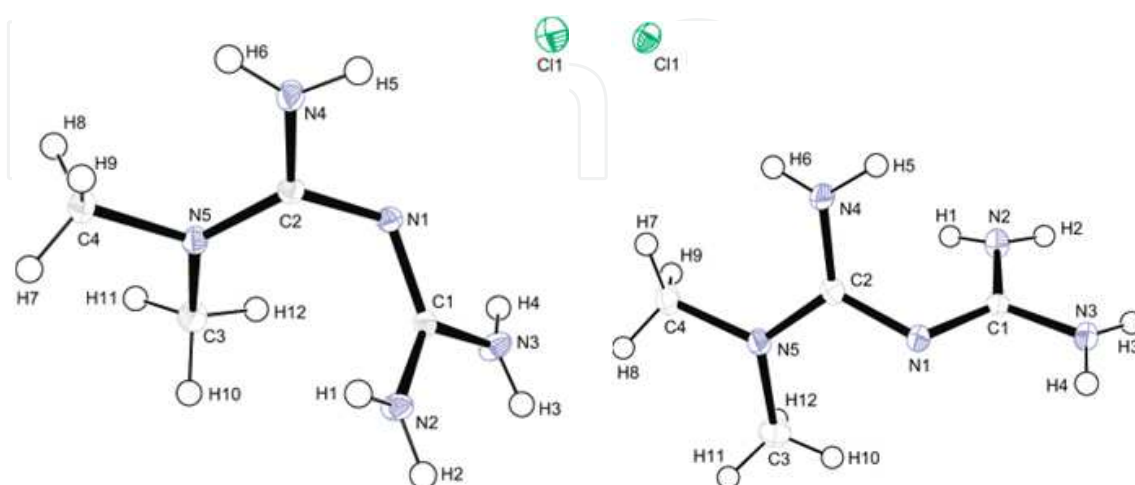


Figure 2. Metformin hydrochloride Form A and B shown, respectively at 50% probability ellipsoids. [50]

6. Thiazolididiones

6.1. Rosiglitazone

Various crystalline forms of maleate salt of rosiglitazone are reported in literature. Choudary *et al.* and Blackler *et al.* put illumination on crystalline hydrates of salt [52-54]. Chebiyyam *et al.* described four crystalline forms (Form I, II, III and IN) while Birari *et al.* described two forms (Form A and B). Form A was detected more stable than B and all the other crystal forms, amorphous form, hydrate and anhydrate converted to Form A [55-56]. Kansalet *al.* depicted three crystal forms (Form I, III and IV) for hydrobromide salt of rosiglitazone and formulated Form III in compacted dosage form, while Greil *et al.* elaborated two hydrates (Form A and C), one solvate (Form D) and three anhydrate (Form B, B1 and E). 1:1 hydrates were recovered which may lose their water content at different temperature. Form B and B1 have shown same melting endotherm temperature but they were distinguished by PXRD [57-58].

6.2. Pioglitazone hydrochloride

Only two polymorphic form I and II has been evaluated which are patented [59].

6.3. Troglitazone

Various crystalline forms of troglitazone are patented. Polymorphs 1,2,3 and 6 are obtained by different modes of recrystallization while form 4 and 5 are derived by heating any one of the form 1, 2, 3 or 6 [60].

7. Dipeptidyl peptidase-4 inhibitor

7.1. Alogliptin

In literature, six crystal forms of tartrate (Form A, B, C, D, E and F) and one crystalline form of benzoate salt of alogliptin (Form A) were reported. Among the crystal forms of alogliptin tartrate, Form A was found to be more stable and all forms during stability studies converted to Form A. The most stable form were analyzed for solubility and also established thermally stable up to 200°C and a variable hydrate.

Form A of benzoate salt was found to be much stable and amorphous form converted to stable Form A during heating [61-62].

7.2. Linagliptin benzoate

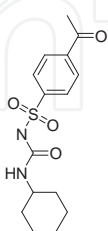
Crystalline forms of linagliptin benzoate have been patented. Form II is less hygroscopic than Form I. Thus, can be easily handled in standard pharmaceutical processing conditions and no special packing is required during its storage [63].

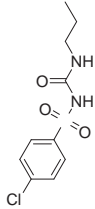
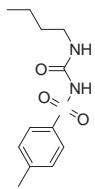
7.3. Sitagliptin

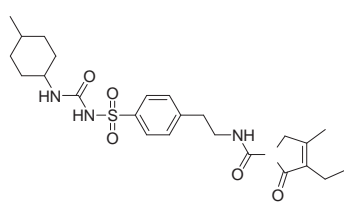
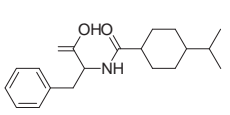
Numerous solvates and crystal forms of sitagliptin phosphate have been patented. All the reported crystalline solvates converted to Form II on desolvation and on heating metastable Form II converted to Form I (at 45°C) and to Form III at 110°C. Form I (stable at higher temperature) and Form III (stable at lower temperature) have enantiotropic relation [64]. Form IV, also a metastable form, slowly converted to crystalline sitagliptin phosphate monohydrate [65]. Huang *et al.* prepared Form V and processed them to pharmaceutical formulation [66].

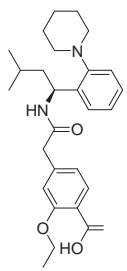
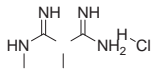
7.4. Saxagliptin

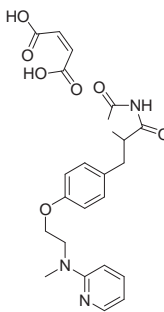
Monohydrate, hemihydrates and mixture of thereof of saxagliptin had been prepared and patented [67]. Nine polymorphic forms of saxagliptin hydrochloride (Form K, T, Z, N, S, O, B, C and D) had been evaluated either from its amorphous form or dihydrate form and being patented. Forms K, S, N and Z are polymorphically pure, Form D is a hydrate, Form T is in a mixture with ammonium chloride, Form O is in a mixture with form K and saxagliptinmonohydrochloridemonohydrate while Form B is in a mixture with saxagliptinmonohydrochloridedihydrate [68]

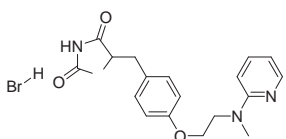
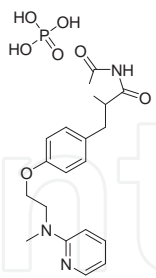
Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
<p>ACETOHEXAMIDE</p> 	Polymorph A	Glacial acetic acid	Slow evaporation	180-183°C	[13]
	Polymorph B	Chloroform	Slow evaporation	183-185°C	
	Form I (triclinic)	Ethanol/ methanol/ acetone	Slow evaporation	187°C	
	Form II (monoclinic)	Ethanol: water (1:1)	Heating, slow evaporation	157°C (T), 186°C (M)	[17]
	CHCl ₃ - II	Hot chloroform	Slow evaporation	164-169°C (T), 182°C (M)	
	Form IV	Hot benzene	Slow evaporation	184-186°C	[19]
	Form II (mixture of I and IV)	Hot Isobutanol	Slow evaporation	176-178°C	[20]
	Form III	Chloroform	Rapid cooling of saturated solution at 55°C	-	
	Form V	-	Heating Form III at 160°C	-	[19]

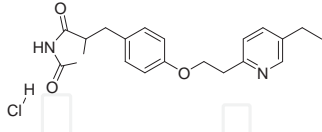
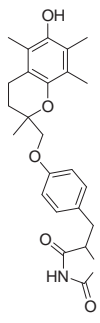
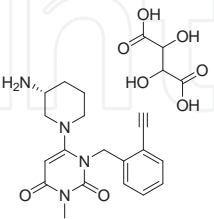
Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
CHLORPROPAMIDE 	Form VI	HP- β -CD in sodium phosphate buffer of pH 8.0	Titration to 0.5 M HCl, filtration, cooling	-	[21]
	Form A/ III/ IV	Ethanol-water mixture	Slow evaporation	121-122°C	
	Form B /II /V	-	Recrystallization from melt of Form A	124-127°C	[22-24]
	Form C /I	-	Heat Form A at 120°C	128-130°C	
	Form IV	Carbon tetrachloride	Slow evaporation	122-123°C	[23]
	Form V	Benzene	Desolvation of benzene solvate	< 118°C	
	Form II	Chloroform	Rapid evaporation	-	[24]
	Form III	Hexanol	Rapid cooling	-	
	Form α (orthorhombic)	Ethanol	Slow evaporation	124°C (T), 127-128°C (M)	[26]
	Form β (orthorhombic)	Heptane-ethyl acetate	Solvent-antisolvent addition	125-127°C	
	Form γ (monoclinic)	Heptanes: ethyl acetate (1:2)	Freezing at -20°C	120°C (T), 128°C (M)	[27]
Form δ (orthorhombic)	Heptanes: ethyl acetate (2:1)	Slow evaporation	124°C (T), 128°C (M)		
Form ϵ (orthorhombic)	-	Solid transformation of Form α	128°C		
TOLBUTAMIDE 	Form I	Benzene: hexane (2:1)	Solvent-antisolvent addition, slow evaporation	127°C	[38]
Form II	-	Form IV stored at 60°C, 75% RH, 10min.	100°C (T), 127°C (M)		

Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
	Form III	Ethanol: water (2:1)	Solvent-antisolvent addition, slow evaporation	113°C (T), 127°C (M)	
	Form IV	Ethanol: DCM (1.2:1)	Spray drying	80°C, 100°C (T), 127°C (M)	
	Form V	Conc. HNO ₃ , methanol	Cocrystallisation with p-nitrophenol, p-phenylenediboric Acid in ethanol	-	[69]
	Form I	Ethanol and chloroform	Slow evaporation	207°C	[43]
	Form II	Ethanol: water (1:1)	Heating, slow evaporation	140°C (T), 207°C (M)	[70]
GLIMEPIRIDE					
	Form I	-	Slow evaporation	174°C	[45]
	Form III	-	Slow evaporation	153°C	[45]
	Solvate	pentanol/ toluene	Slow evaporation	109°C	[44]
	New Form	-	Sublimation of glassy state at 130-160 °C	218 °C	[46]
	Glassy form	-	Quench cooling of melt	42- 56°C (T), 90-135°C (exotherm), 198°C (M)	[46]
GLIBENCLAMIDE	Form B	Methanol: water (7:3)	Cooling at 10°C	128-130°C	[71]
	Form H	Acetone: water (2:3)	Cooling at 10°C	138-141°C	[71]
	Form S	-	Melting/ isothermal treatment of Form B/H	172 °C	[48]
NATEGLINIDE					
	Form S	-	Melting/ isothermal treatment of Form B/H	172 °C	[48]

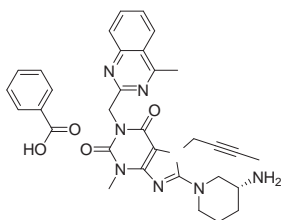
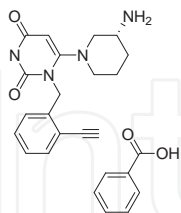
Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
S-REPAGLINIDE 	Form I	Ethanol/water (2:1), acetone/pet ether, methanol/water, THF/MTBE, ethyl acetate/pet ether, n-propanol/water, ACN/water, MIBK/MTB, diethyl ketone/MTB, t-butanol/water, methyl ethyl ketone/n-heptane, diglyme/n-heptane, methyl ethyl ketone/MTBE, 1,4-dioxane/n-heptane, n-butanol/MTBE, chloroform/n-hexane	Solvent-antisolvent, slow evaporation	130-131°C	[49]
	Form II	Pet ether: toluene (5:3)	Rapid cooling	99-101°C	
	Form III (from Form I, II and amorphous form)	Toluene	Heating followed by cooling	80-84°C	
METFORMIN HYDROCHLORIDE 	Form A	Methanol: water (2:1)	slow evaporation	-	[50]
	Form B	Acetone: water (3:1)	slow evaporation	-	
ROSIGLITAZONE MALEATE	Hydrate	Acetonitrile: water (30:1)/ THF: water	Heating followed by cooling	-	[52]

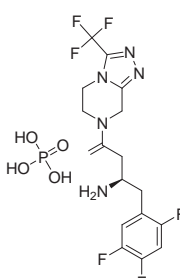
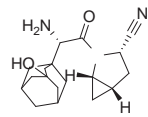
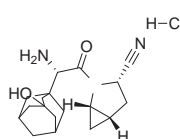
Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
	Hydrate	(30:1)/ methyl ethyl ketone: water (30:1)/ ethyl acetate: water (100:1)/ isopropanol: water (33:1)			
		Ethanol and water (2.1%v/v)	Heating followed by cooling		
		Methanol-water/ acetonitrile- water/ ethanol- water	Heating followed by cooling		
		Methanol-water	Heating followed by cooling	-	[53-54]
	Form I	Ethanol	Heating followed by cooling	100.53°C	
	Form II	Acetone	Heating followed by cooling	127.67°C	
	Form III	Methanol	Heating followed by cooling	126.41°C	[55]
	Form IN	1,4-dioxane	Heating followed by cooling	125.39°C	
	Form A	Methanol-ethyl acetate	Heating solution in methanol followed by addition of ethyl acetate		
	Form B	Isopropyl alcohol	Heating followed by cooling	-	[56]

Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
		Methanol	Addition of methanol to acetone solution of salt		
		Isopropyl alcohol / THF	Heating of Suspension of Form A followed by cooling		
		-	Heating followed by cooling		
ROSIGLITAZONE HYDROBROMIDE	Form I	Acetone	Reflux, cooling	-	
	Form III	Demineralised water	Reflux, cooling	-	[57]
	Form IV	Acetone	Heating Form I in acetone	-	
	Form A	Acetone and water	Stirring of suspension	171-177°C	
		Ethanol and water	Stirring of suspension		
	Form B	Acetone and water	Stirring of suspension	175-176°C	
ROSIGLITAZONE PHOSPHATE	Form B1	-	Stirring of suspension	175-176°C	
	Form C	Acetone: water (1:1)	Phosphoric acid added to solution of Form B	-	[58]
			Stirring of suspension of Form A		
	Form D	Methanol	Heating of suspension of Form A	-	
	Form E	Ethanol	Heating followed by cooling	167-172°C	
PIOGLITAZONE HYDROCHLORIDE	Form I	DMF/ Methanol/ acetic acid	Heating followed by cooling	198°C	[59]

Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
 TROGLITAZONE 	Form II	Acetic acid, water	Heating followed by cooling	183°C	
	Form 1	Benzene: acetone (100: 1)	Slow evaporation	179°C	
	Form 2	Benzene extraction, DCM added	Fast evaporation at -10°C	110°C (T), 175°C (M)	
	Form 3	Acetone: benzene (1:2)	Cooling at 5°C	185°C	
	Form 4	-	Form I heated to melt	56°C (T), 110 °C (exotherm), 177°C (M)	[60]
	Form 5	-	Heating of Form IV at 130 °C	157°C (exotherm), 180°C (M)	
	Form 6	Acetone: benzene (1:4)	Cooling of solution of Form I at 5 °C	105°C	
		Acetone: water (2:3) or methanol	Filtration, slow evaporation		
			Cold acetone/ toluene was added in filtered solution of hot methanol and alogliptin tartrate, slow evaporation		
ALOGLIPTIN TARTRATE 	Form A	Hot methanol and acetone/ methanol and toluene	Heating, slow evaporation	172.5°C	[61]
		water	Heating, slow evaporation		
	Form B	Tetrahydrofuran: water (2:1)/ dioxane: water (2:1) / acetonitrile: water (4:3)	Filtration, slow evaporation	124.4°C	

Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
	Form C	Ethanol: water (1:1) / isopropanol: water (1:1)	Filtration, slow evaporation	122.4°C	
		water	Heating at 80°C, filtered and cooling		
	Form D	methanol	Placed amorphous form with methanol in sealed chamber for several weeks	173.3°C	
			Water: acetonitrile (4:21) / water: dioxane (2:1)	Heating at 50°C, filtered, slow evaporation	
	Form E	-	Placed amorphous form with saturated salt solution at 84% RH in sealed chamber	-	
	ALOGLIPTIN BENZOATE	Form A	Acetone / Methanol	Filtration, fast evaporation	
Acetonitrile			Heating slurry at 60°C, filtration, slow evaporation		
Ethanol: isopropyl acetate (99:1)			Reflux, cooling		
LINAGLIPTIN BENZOATE	Form I	Isopropanol	Slow evaporation	-	[63]
	Form II	Acetonitrile	Slow evaporation	193°C	



Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
SITAGLIPTIN PHOSPHATE 	Solvate	Methanol/ ethanol/ 1-propanol/ 2-propanol/ acetone/ acetonitrile	By contacting with solvent for 5 minutes	213.61°C	[64]
	Form I	Isoamyl alcohol/ water	Slow evaporation	215.37°C (T), 217.27°C (M)	
	Form II	-	Desolvation of ethanol solvate	114.6°C (T), 213.80°C (M)	
	Form III	Isoamyl alcohol/ water	Slow evaporation	80.90°C (T), 215.94°C (M)	
	Form IV	-	Heating monohydrate form above 58°C	213.3°C	[65]
Form V	Methanol-water/ acetone-water	Methanol, n-butanone, THF, ACN, DMC and water	Heating followed by cooling Distillation at 55°C	214.88°C	[66]
SAXAGLIPTIN 	Form H-1 (monohydrate)	Ethanol Dibutylether Water, 80% RH	Kept in desiccator in atmosphere of respective solvents	-	[67]
SAXAGLIPTIN HYDROCHLORIDE 	Form K	Ethyl acetate, Conc. HCl	Reflux, cooling	-	
	Form T	Saturated ammonium chloride pH 4.53	Precipitation	-	
	Form Z (Dihydrate)	Ethyl alcohol, Methylisopropyl ketone	Precipitation	-	[68]
	Form N	2- butanol	Reflux, cooling	-	
Form S	Wet ethyl acetate, Conc. HCl	Heating followed by cooling	-		

Drug	Crystal form	Solvent used	Method of preparation	Transition (T)/ Melting endotherms(M)	References
	Form O	0.8 M HCl/ Ethyl alcohol	Heating followed by cooling	-	
	Form B	Ethyl alcohol, Methyl ethyl ketone	stirring	-	
	Form C	Propyl alcohol	Heating followed by cooling	-	
	Form D (hydrate)	1-butanol	Heating, stirring	-	

Table 1. Crystalline Forms of Antidiabetics

8. Conclusion

The crystallization process has profound impact on crystal forms, which further affect biopharmaceutical properties of pharmaceutical solids. Various crystal forms of antidiabetics have been reported in literature and some have even gained the status of a patent. The existence of these different crystal forms are possible due to presence of sulphoxamide, carboxamide, thiazolidendione, etc. groups in these agents. For the optimized pharmaceutical acceptable solid form, one must be cognizant of the potentiality of an API to exist in various crystal forms by altering the crystallization conditions. Because of this, screening of new crystal forms of API's has become a vital part of drug discovery and development in past decade.

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